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JC20 Rec'd PCT/PTO 01 MAR 2002

FORM PTO-1390 (REV 10-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER 6783-01WOUS	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/070177		PRIORITY DATE CLAIMED 01 SEPTEMBER 1999	
INTERNATIONAL APPLICATION NO. PCT/SE00/01683	INTERNATIONAL FILING DATE 01 SEPTEMBER 2000		
TITLE OF INVENTION Use of at least one substance based on nicotine and/or a substance produced from said one substrate for the manufacture of a medicament and a method for treatment of obstructive			
APPLICANT(S) FOR DO/EO/US László Bense			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)). 4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(3)). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).			
Items 11 to 16 below concern document(s) or information included:			
11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input type="checkbox"/> Other items or information:			

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Ana R. Rivera

(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Ana R. Rivera

(SIGNATURE OF PERSON MAILING PAPER OR FEE)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/070177		INTERNATIONAL APPLICATION NO. PCT/SE00/01683		ATTORNEY'S DOCKET NUMBER 6783-01WOUS	
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<p>17. <input checked="" type="checkbox"/> The following fees are submitted:</p> <p>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</p> <p>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO. \$890.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00</p> <p>International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00</p> <p>International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00</p> <p style="text-align: right;">ENTER APPROPRIATE BASIC FEE AMOUNT =</p> <p>Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).</p> <table border="1" style="width:100%; border-collapse: collapse;"> <tr> <th style="width:15%;">CLAIMS</th> <th style="width:20%;">NUMBER FILED</th> <th style="width:20%;">NUMBER EXTRA</th> <th style="width:20%;">RATE</th> <th style="width:10%;"></th> <th style="width:15%;"></th> </tr> <tr> <td>Total claims</td> <td>11 - 20 =</td> <td>0</td> <td>X \$18.00</td> <td>\$</td> <td></td> </tr> <tr> <td>Independent claims</td> <td>1 - 3 =</td> <td>0</td> <td>X \$84.00</td> <td>\$</td> <td></td> </tr> <tr> <td colspan="3">MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td>+ \$280.00</td> <td>\$</td> <td></td> </tr> <tr> <td colspan="4" style="text-align: right;">TOTAL OF ABOVE CALCULATIONS =</td> <td>\$ 1040.00</td> <td></td> </tr> </table> <p><input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.</p> <p style="text-align: right;">SUBTOTAL =</p> <p>Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).</p> <p style="text-align: right;">TOTAL NATIONAL FEE =</p> <p>Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +</p> <p style="text-align: right;">TOTAL FEES ENCLOSED =</p> <table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td rowspan="2" style="width:60%;"></td> <td style="width:20%;">Amount to be refunded:</td> <td style="width:20%;">\$</td> </tr> <tr> <td>charged:</td> <td>\$</td> </tr> </table>	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE			Total claims	11 - 20 =	0	X \$18.00	\$		Independent claims	1 - 3 =	0	X \$84.00	\$		MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$280.00	\$		TOTAL OF ABOVE CALCULATIONS =				\$ 1040.00			Amount to be refunded:	\$	charged:	\$	<p style="text-align: center;">CALCULATIONS PTO USE ONLY</p>
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a. ☒ A check in the amount of \$ 520.00 to cover the above fees is enclosed.

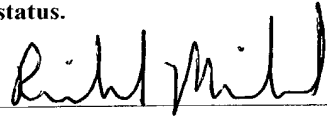
b. ☐ Please charge my Deposit Account No. 13-0235 in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-0235. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Richard R. Michaud
McCormick, Paulding & Huber LLP
CityPlace II
185 Asylum Street
Hartford, CT 06103-3402
(860) 549-5290



SIGNATURE

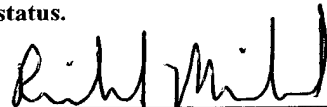
Richard R. Michaud March 1, 2002

NAME

40,088

REGISTRATION NUMBER

DUPLICATE

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/070177		INTERNATIONAL APPLICATION NO. PCT/SE00/01683		ATTORNEY'S DOCKET NUMBER 6785-01WOUS	
17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
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SUBTOTAL =				\$ 520.00	
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TOTAL FEES ENCLOSED =				\$ 520.00	
				Amount to be refunded:	\$
				charged:	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>520.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>13-0235</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>13-0235</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: Richard R. Michaud McCormick, Paulding & Huber LLP CityPlace II 185 Asylum Street Hartford, CT 06103-3402 (860) 549-5290			 SIGNATURE Richard R. Michaud March 1, 2002 NAME 40,088 REGISTRATION NUMBER		

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Ana R. Rivera

(TYPED OR PRINTED NAME OF PERSON MAILING
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of)
)
László Bense)
)
on USE OF AT LEAST ONE SUBSTANCE)
BASED ON NICOTINE AND/OR A)
SUBSTANCE PRODUCED FROM SAID...)
)
Serial No.: National Stage Entry of)
Int'l Appln. No. : PCT/SE00/01683)
International Filing Date: 1 September 2000)
Filed: Simultaneously herewith) (Our Docket No. 6783-01WOUS)

Hartford, Connecticut, March 1, 2002

Box PCT
Assistant Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

S I R:

Prior to examination on the merits, please amend the above-identified
application as follows:

In the Specification:

Page 1

Please insert after the Title the following paragraph:

Cross-Reference to Related Applications:

This application is entitled to the benefit of and incorporates by reference essential subject matter disclosed in International Patent Application No. PCT/SE00/01683, International Filing Date September 1, 2000; Swedish Application No. 9903085-0, filed on 1 September 1999; and Swedish Application No. 0001075-1, filed on 27 March 2000.

Please replace the first paragraph with the following paragraph:

The present invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to human beings or animals. The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases in human beings or animals.

Please replace the last paragraph that begins on page 1 and ends on page 2, with the following paragraph:

During normal inhalation the bronchi are expanded, which counteracts the obstruction to a certain extent. During the following exhalation the lung tissue is compressed, including the bronchi, and a somewhat smaller gas volume may therefore flow through the respiratory tract. This leads to a valve effect when a certain balance arises. By a certain overpressure in the respiratory tracts and the lung, the obstruction may be overcome and the inhaled gas volume be emptied. The pressure in the lung is however not sufficient for completely emptying the lung. There is always a certain amount of air (residual volume; normally about 500 ml of an adult) in the lung after the first breath. This balance depends inter alia on and is influenced by the ambient air pressure; the greater the pressure the weaker the respiratory tracts, especially for early born, immature children.

Page 2

Please replace the second paragraph with the following paragraph:

During smoking the mucous membrane in the respiratory tracts and bronchi is irritated, which leads to a swelling of the mucous membrane. This swelling decreases the lumen of the respiratory tracts, i.e. the obstruction arises and thus the air flow in the respiratory tracts is restrained. This leads to an increase in valve effect, resulting in a higher pressure in the respiratory tracts and the lung, and to a larger residual volume in the lung. The increase also leads to a destruction of tissue, which further reduces the gas exchange, i.e. the breathing capacity. If nicotine or nicotine-like substances are supplied, not via the respiration, a vessel contracting, decongestant effect, which reduces the obstruction, is obtained.

Please replace the third paragraph which begins on page 2 and ends on page 3, with the following paragraph:

Pulmonary barotrauma appears from tissue destruction caused by the above-described inner pressure. Pulmonary barotrauma may principally refer to one single alveolus or a smallest respiratory tract, or several small alveoli within the lung. If this tissue destruction process is expanded to the whole lung it is called pulmonary emphysema. In the cases when air is collected diffusely in the lung tissue proper, we have an interstitial emphysema or in a delimited way, a bulla (blister). If the air is collected adjacent to the pleura in a delimited manner we have a subpleural bleb. The air may also come to the intrapulmonary space and we have a so-called pneumomediastinum or into the heart sack; pneumopericardium. If the tissue destruction is expanded so that the pleura is destroyed, we have a spontaneous pneumothorax (SP). With regard to the fact that pathophysiological changes in the lung are documented in case of SP, it is not any longer relevant to call SP a disease of the pleura.

Page 3

Please replace the first full paragraph with the following paragraph:

The obstruction leads to an expansion in one part of a lung and thus compression in the surrounding remaining portion of the lung. Such an expansion and compression is irreversible for a smoker even if he would stop smoking. If the surrounding compressed lung part is very large, surgery could be considered for removing a large significant blister and thus create space for the respiratory work. However, it is very rare that a patient is suitable for such an operation, whereby an expected effect is far from being optimal.

Page 4

Please replace the second, third and fourth full paragraphs with the following paragraphs:

This object is obtained by the use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to human beings or animals for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.

The applicant has realised that nicotine, if it is not supplied via the respiration, has an inhibitory effect on the development of respiratory tract obstruction followed by the irreversible substance loss, elasticity loss and expansion of the lung tissue, i.e. the negative effects arising from pulmonary emphysema, pulmonary barotrauma and spontaneous pneumothorax. By supplying nicotine to the body of the persons suffering from pulmonary emphysema, it is possible to prevent or limit the development of the disease. Nicotine also ought to have a prophylactic effect, i.e. the origin of pulmonary emphysema of persons having a risk to be effected by this disease, for instance smokers, which have stopped smoking, may be prevented by the supply of nicotine, however not via the bronchi, respiratory organs.

The definition of at least one substance based on nicotine and/or a substance produced from said one substance is to be given a broad interpretation and in this definition are included substantially pure nicotine, nicotine compounds, nicotine related compounds, nicotine derivatives, intermediate metabolites of nicotine and/or nicotine compounds, degradation products from

nicotine or nicotine compounds with completely or partly identical, similar effects.

Page 6

Please replace the second paragraph with the following paragraph:

The object is also obtained by a method for prophylactic or therapeutic treatment of obstructive lung diseases of human beings or animals, wherein said individual is supplied with a nicotine-based substance.

In the claims:

Please cancel all of the claims of the application, namely claims 1-20, and add the following new claims 21-31:

21. (New) A medicament for counteracting obstructive lung disease comprising a therapeutically effective amount of at least one substance based on nicotine and a pharmaceutically acceptable carrier, adjuvant or diluent.

22. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is supplied via the blood path.

23. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered via the gastrointestinal tract.

24. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered transdermally.

25. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered intravascularly.

26. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered intranasally.

27. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered intravaginally.

28. (New) The medicament according to claim 1 wherein the at least one nicotine based substance includes substantially pure nicotine.

29. (New) The medicament according to claim 1 wherein the at least one nicotine based substance includes nicotine derivatives, intermediate metabolite of nicotine, or degradation products of nicotine.

30. (New) The medicament according to claim 1 wherein the at least one nicotine based substance is absorbed by a binding agent.

31. (New) The medicament according to claim 1 wherein the therapeutically effective amount of at least one nicotine based substance is administered to a mammal having a congenital bilateral bronchial anomaly.

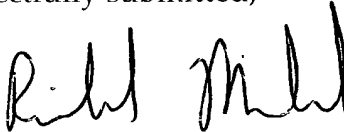
REMARKS

The above amendments are being made to place the application in better form for prosecution, to include the amended claims of the International Application, and to remove multiple dependencies from its claims.

Should the Examiner have any questions regarding the present application, Applicant respectfully requests that the Examiner contact Applicants' representative at the phone number listed below. While Applicant believes no

fees are due with the filing of this amendment, please charge any deficiencies in fees associated with this filing to our Deposit Account No. 13-0235.

Respectfully submitted,

By 

Richard R. Michaud
Registration No. 40,088
Attorney for Applicant

McCormick, Paulding & Huber LLP
CityPlace II
185 Asylum Street
Hartford, Connecticut 06103-3402
(860) 549-5290

- 5 Use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament, and a method for treatment of obstructive lung diseases

10 THE BACKGROUND OF THE INVENTION AND PRIOR ART

The present invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to
15 ~~an individual of a human being¹ or an animal²~~ The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases ~~of in individual of a human being³ or an animal⁴~~

- 20 Pulmonary emphysema is a common disease, which in particular affects smokers. The disease is characterised by a permanent expansion and destruction of the finest bronchi and the walls of the alveoli. Pulmonary emphysema is a very serious disease and the destruction process is irreversible so that the disease leads to
25 increasing respiratory difficulties.

Pulmonary emphysema belongs to a group of diseases usually called obstructive lung diseases due to the fact that the disease obstructs the flow in the respiratory tracts. The obstruction is the
30 underlying cause also to pulmonary barotrauma, including spontaneous pneumothorax. These diseases have symptoms and localised effects to the lung tissue similar to pulmonary emphysema.

- 35 During normal inhalation the bronchi are expanded, which counteracts the obstruction to a certain extent. During the following exhalation the lung tissue is compressed, including the bronchi, and

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greater the pressure

a somewhat smaller gas volume may therefore flow through the respiratory tract. This leads to a valve effect when a certain balance arises. By a certain overpressure in the respiratory tracts and the lung, the obstruction may be overcome and the inhaled gas volume be emptied. The pressure in the lung is however not sufficient for completely emptying the lung. There is always a certain amount of air (residual volume; normally about 500 ml of an adult) in the lung after the first breath. This balance depends inter alia on and is influenced by the ambient air pressure; the more the weaker the respiratory tracts, especially for early born, immature children.

During smoking the mucous membrane in the respiratory tracts and bronchi is irritated, which leads to a swelling of the mucous membrane. This swelling decreases the lumen of the respiratory tracts, i.e. the obstruction arises and thus the air flow in the respiratory tracts is restrained. This leads to an increase of the so-called valve effect, to a higher pressure in the respiratory tracts and the lung, and to a larger residual volume in the lung. The increase also leads to a destruction of tissue, which further reduces the gas exchange, i.e. the breathing capacity. If nicotine or nicotine-like substances are supplied, not via the respiration, a vessel contracting, decongestant effect, which reduces the obstruction, is obtained.

resulting in 15 *above-described* 20 *from* 25 Pulmonary barotrauma appears ~~due to such a~~ tissue destruction *caused* by the inner pressure. Pulmonary barotrauma may principally refer to one single alveolus or a smallest respiratory tract, or several small alveoli within the lung. If this tissue destruction process is expanded to the whole lung it is called pulmonary emphysema. In the cases when air is collected diffusely in the lung tissue proper, we have an interstitial emphysema or in a delimited way, a bulla (blister). If the air is collected adjacent to the pleura in a delimited manner we have a subpleural bleb. The air may also come to the intrapulmonary space and we have a so-called pneumomediastinum or into the heart sack; pneumopericardium. If the tissue destruction is expanded so that the pleura is destroyed, we have a spontaneous pneumothorax (SP). With regard to the fact that

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3

remaining part of the

pathophysiological changes in the lung are documented in case of SP, it is not any longer relevant to call SP a disease of the pleura.

5 The obstruction leads to an expansion in ^{in the} ~~a lung part~~ ^{one part of a} and thus to a compression of the surrounding lung ~~part~~. Such an expansion and compression is irreversible for a smoker even if he would stop smoking. If the surrounding compressed lung part is very large, surgery could be considered for removing a large significant blister and thus create space for the respiratory work. However, it is very
10 rare that a patient is suitable for such an operation, whereby an expected effect is far from being optimal.

15 The destruction of tissue may be localised to the upper part of the lung, due to bronchial anomaly at spontaneous pneumothorax or to the lower part of the lung at alfa-1-antitrypsin AAT-deficiency. AAT is an enzyme protecting the elastic fibres of the lung. The fibres are subjected to the largest load in the lower part, where the largest expansion of the lung takes place when we breathe. If the protecting effect ceases, the elasticity is lost and this can be easily
20 seen on the most stressed tissue part.

The destruction may also be general without anomaly or AAT-deficiency due to smoking.

25 Bilateral bronchial anomaly is an anatomical congenital obstruction with a characteristically changed branching structure of the respiratory tracts and this obstruction may be increased by smoking. Bilateral bronchial anomaly may today be shown by diagnostic methods known per se, for instance by means of X-ray
30 pictures disclosing the bronchial structure of a patient. The respiratory tracts consist of bronchi, which from the main bronchus are divided to smaller and smaller bronchi. The first bronchus forms the bronchus of the first generation, the bronchi after the first division are called the bronchi of the second generation, after the
35 second division the bronchi of the third generation, etc. Bilateral bronchial anomaly means that the bronchi of the third generation are missing in an individual and are replaced by very characteristic,

(Marked-up Version)

irregular narrowing connections. The air exchange to and especially from the alveoli will thus be hampered by this defect bronchial structure, which is identifiable.

5 SUMMARY OF THE INVENTION

The object of the present invention is to provide a means, which counteracts such obstructive lung diseases in a prophylactic or therapeutic manner.

10

This object is obtained by the use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to ~~an individual of a human being or an animal~~ for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.

15

The applicant has realised that nicotine, if it is ^{not} supplied via the respiration, has an inhibitory effect on the development of respiratory tract obstruction followed by the irreversible substance loss, elasticity loss and expansion of the lung tissue, i.e. the negative effects arising from pulmonary emphysema, pulmonary barotrauma and spontaneous pneumothorax. By supplying nicotine to the body of the persons suffering ~~by~~ pulmonary emphysema, it is thus possible to prevent or ~~to~~ limit the development of the disease.

20

Nicotine also ought to have a prophylactic effect, i.e. the origin of pulmonary emphysema of persons having a risk to be effected by this disease, for instance smokers, which have stopped smoking, may be prevented by the supply of nicotine, however not via the bronchi, respiratory organs.

25

The definition ^{of} at least one substance based on nicotine and/or a substance produced from said one substance is to be given a broad interpretation and in this definition are included substantially pure nicotine, nicotine compounds, nicotine related compounds, nicotine derivatives, intermediate metabolites of nicotine and/or nicotine compounds, degradation products from nicotine or nicotine compounds with completely or partly identical, similar effects.

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(Marked up version)

According to a further embodiment of the invention, the use is intended for said individual, which has a congenital bilateral bronchial anomaly. As mentioned initially, the destruction of the lung tissue, due to smoking, may be general without anomaly or due to AAT-deficiency. The applicant has however realised that the risk of serious obstructions in the lungs, which leads to pulmonary barotrauma, such as spontaneous pneumothorax and pulmonary emphysema, is substantially higher for smokers having a congenital bilateral bronchial anomaly than for smokers not having such an anomaly. This risk ought to be in the order of 2000-3000 % higher for smokers with, than smokers without bilateral bronchial anomaly. The formed structure of a bilateral bronchial anomaly is associated with a different function, such as ventilation, perfusion, and a high sensibility for external factors, such as smoking.

The object is also obtained by a method for prophylactic or therapeutic treatment of obstructive lung diseases of an individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.

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DESCRIPTION OF EMBODIMENTS OF THE INVENTION

Investigations have been made showing an inverted correlation between smoking habits of pregnant women and the risk of pulmonary barotrauma of the new-born children of the women. Thus, new-born children of smoking women have a lower predisposition to get pulmonary barotrauma than new-born children of women which are not smoking. Investigations also show that foetuses of women which smoke have nicotine in the blood. This inverted relation thus indicates that nicotine may counteract obstructive lung diseases.

It is known to use nicotine, i.e. 3-(1-methyl-2-pyrrolidyl) pyridine for smoking cessation, i.e. for reducing the abstinence complaints. The use now proposed according to the present invention may thus be regarded as a second medical indication. The medical effect mentioned above may be obtained for smokers which are smoking,

(MARKED-UP VERSION)

- 5 Use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament, and a method for treatment of obstructive lung diseases

10 THE BACKGROUND OF THE INVENTION AND PRIOR ART

The present invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to
15 an individual of a human being or an animal. The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases of in individual of a human being or an animal.

20 Pulmonary emphysema is a common disease, which in particular affects smokers. The disease is characterised by a permanent expansion and destruction of the finest bronchi and the walls of the alveoli. Pulmonary emphysema is a very serious disease and the destruction process is irreversible so that the disease leads to
25 increasing respiratory difficulties.

Pulmonary emphysema belongs to a group of diseases usually called obstructive lung diseases due to the fact that the disease obstructs the flow in the respiratory tracts. The obstruction is the
30 underlying cause also to pulmonary barotrauma, including spontaneous pneumothorax. These diseases have symptoms and localised effects to the lung tissue similar to pulmonary emphysema.

35 During normal inhalation the bronchi are expanded, which counteracts the obstruction to a certain extent. During the following exhalation the lung tissue is compressed, including the bronchi, and

a somewhat smaller gas volume may therefore flow through the respiratory tract. This leads to a valve effect when a certain balance arises. By a certain overpressure in the respiratory tracts and the lung, the obstruction may be overcome and the inhaled gas volume
5 be emptied. The pressure in the lung is however not sufficient for completely emptying the lung. There is always a certain amount of air (residual volume; normally about 500 ml of an adult) in the lung after the first breath. This balance depends inter alia on and is influenced by the ambient air pressure; the more the weaker the
10 respiratory tracts, especially for early born, immature children.

During smoking the mucous membrane in the respiratory tracts and bronchi is irritated, which leads to a swelling of the mucous membrane. This swelling decreases the lumen of the respiratory
15 tracts, i.e. the obstruction arises and thus the air flow in the respiratory tracts is restrained. This leads to an increase of the so-called valve effect, to a higher pressure in the respiratory tracts and the lung, and to a larger residual volume in the lung. The increase also leads to a destruction of tissue, which further reduces the gas
20 exchange, i.e. the breathing capacity. If nicotine or nicotine-like substances are supplied, not via the respiration, a vessel contracting, decongestant effect, which reduces the obstruction, is obtained.

25 Pulmonary barotrauma appears due to such a tissue destruction by the inner pressure. Pulmonary barotrauma may principally refer to one single alveolus or a smallest respiratory tract, or several small alveoli within the lung. If this tissue destruction process is expanded to the whole lung it is called pulmonary emphysema. In the cases
30 when air is collected diffusely in the lung tissue proper, we have an interstitial emphysema or in a delimited way, a bulla (blister). If the air is collected adjacent to the pleura in a delimited manner we have a subpleural bleb. The air may also come to the intrapulmonary space and we have a so-called pneumomediastinum
35 or into the heart sack; pneumopericardium. If the tissue destruction is expanded so that the pleura is destroyed, we have a spontaneous pneumothorax (SP). With regard to the fact that

pathophysiological changes in the lung are documented in case of SP, it is not any longer relevant to call SP a disease of the pleura.

5 The obstruction leads to an expansion in a lung part and thus to a compression of the surrounding lung part. Such an expansion and compression is irreversible for a smoker even if he would stop smoking. If the surrounding compressed lung part is very large, surgery could be considered for removing a large significant blister and thus create space for the respiratory work. However, it is very
10 rare that a patient is suitable for such an operation, whereby an expected effect is far from being optimal.

The destruction of tissue may be localised to the upper part of the lung, due to bronchial anomaly at spontaneous pneumothorax or to
15 the lower part of the lung at alfa-1-antitrypsin AAT-deficiency. AAT is an enzyme protecting the elastic fibres of the lung. The fibres are subjected to the largest load in the lower part, where the largest expansion of the lung takes place when we breathe. If the protecting effect ceases, the elasticity is lost and this can be easily
20 seen on the most stressed tissue part.

The destruction may also be general without anomaly or AAT-deficiency due to smoking.

25 Bilateral bronchial anomaly is an anatomical congenital obstruction with a characteristically changed branching structure of the respiratory tracts and this obstruction may be increased by smoking. Bilateral bronchial anomaly may today be shown by diagnostic methods known per se, for instance by means of X-ray
30 pictures disclosing the bronchial structure of a patient. The respiratory tracts consist of bronchi, which from the main bronchus are divided to smaller and smaller bronchi. The first bronchus forms the bronchus of the first generation, the bronchi after the first division are called the bronchi of the second generation, after the
35 second division the bronchi of the third generation, etc. Bilateral bronchial anomaly means that the bronchi of the third generation are missing in an individual and are replaced by very characteristic,

irregular narrowing connections. The air exchange to and especially from the alveoli will thus be hampered by this defect bronchial structure, which is identifiable.

5 SUMMARY OF THE INVENTION

The object of the present invention is to provide a means, which counteracts such obstructive lung diseases in a prophylactic or therapeutic manner.

10

This object is obtained by the use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to an individual of a human being or an animal for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.

15

The applicant has realised that nicotine, if it is not supplied via the respiration, has an inhibitory effect on the development of respiratory tract obstruction followed by the irreversible substance loss, elasticity loss and expansion of the lung tissue, i.e. the negative effects arising from pulmonary emphysema, pulmonary barotrauma and spontaneous pneumothorax. By supplying nicotine to the body of the persons suffering by pulmonary emphysema, it is thus possible to prevent or delimit the development of the disease.

20

Nicotine also ought to have a prophylactic effect, i.e. the origin of pulmonary emphysema of persons having a risk to be effected by this disease, for instance smokers, which have stopped smoking, may be prevented by the supply of nicotine, however not via the bronchi, respiratory organs.

25

The definition at least one substance based on nicotine and/or a substance produced from said one substance is to be given a broad interpretation and in this definition are included substantially pure nicotine, nicotine compounds, nicotine related compounds, nicotine derivatives, intermediate metabolites of nicotine and/or nicotine compounds, degradation products from nicotine or nicotine compounds with completely or partly identical, similar effects.

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Nicotine acts via nicotine receptors partly in the vegetative system and partly in the muscles. The nicotine has firstly an irritating (vasoconstrictive) effect on the blood vessels. The vasoconstriction
5 leads to a decongestion of the mucous membrane in the respiratory tracts, which counteracts the obstruction. If nicotine is supplied in significantly higher doses than intended by the present invention, a paralysis (vessel relaxion) arises via the vegetative ganglions and the central nervous system.

10

According to an embodiment of the invention, the nicotine is to be supplied via the blood. It is essential that the nicotine reaches the lungs via the blood and not via the respiration. The positive effect of nicotine to the disease pulmonary emphysema can thus not be
15 obtained if nicotine is supplied via tobacco smoke. However, it is not excluded that nicotine has a positive effect if it is supplied to the blood immediately at the same time as the patient is smoking even if the positive effect in this case will be reduced.

20 According to a further embodiment of the invention, the nicotine may be administered via the gastrointestinal tract, transdermally, intravascularly, intranasally or intravaginally. The nicotine may thus be supplied in various manners except via the respiratory tracts and the lungs. For instance, the nicotine may be supplied by means of
25 plasters, spray, suppository, pills to be swallowed or in the form of chewable tablets or oral tablets, which are known in connection with smoking cessation. According to a further example, the nicotine may be administered by means of inhalation in such a way that most of the nicotine is taken up by the mucous membranes in the
30 mouth (gastrointestinal tract).

According to a further embodiment of the invention, said substance based on nicotine and/or substances produced by said one substance are absorbed in a binding agent. Such a binding agent
35 may permit a slow administration of the active nicotine substance, so-called "slow release".

According to a further embodiment of the invention, the use is intended for said individual, which has a congenital bilateral bronchial anomaly. As mentioned initially, the destruction of the lung tissue, due to smoking, may be general without anomaly or
5 due to AAT-deficiency. The applicant has however realised that the risk of serious obstructions in the lungs, which leads to pulmonary barotrauma, such as spontaneous pneumothorax and pulmonary emphysema, is substantially higher for smokers having a congenital
10 bilateral bronchial anomaly than for smokers not having such an anomaly. This risk ought to be in the order of 2000-3000 % higher for smokers with, than smokers without bilateral bronchial anomaly. The formed structure of a bilateral bronchial anomaly is associated with a different function, such as ventilation, perfusion, and a high sensibility for external factors, such as smoking.

15 The object is also obtained by a method for prophylactic or therapeutic treatment of obstructive lung diseases of an individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.

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25 pulmonary barotrauma of the new-born children of the women. Thus, new-born children of smoking women have a lower predisposition to get pulmonary barotrauma than new-born children of women which are not smoking. Investigations also show that fetuses of women which smoke have nicotine in the blood. This
30 inverted relation thus indicates that nicotine may counteract obstructive lung diseases.

It is known to use nicotine, i.e. 3-(1-metyl-2-pyrrolidyl) pyridine for smoking cessation, i.e. for reducing the abstinence complaints. The
35 use now proposed according to the present invention may thus be regarded as a second medical indication. The medical effect mentioned above may be obtained for smokers which are smoking,

smokers which are giving up their smoking, smokers which have giving up their smoking until this disease risk is reduced, individuals with a lung obstruction and when one wishes to reduce the obstruction in remaining parts of the lungs and/or no other treatment is available.

It is of course important that the quantity of nicotine supplied is adapted to the individual to receive the medicament. A suitable dosing for obtaining the desired effect may be 1-100 mg/24h, preferably 5-50 mg/24h, for instance 7mg/24h, 14mg/24h or 21mg/24h. These doses refer to a medicament with nicotine in substantially pure form.

Such a dose may for instance be obtained by means of tablets of the type called "slow release". Such tablets may contain a binding agent permitting a slow release of the active nicotine substance. The tablets are suitably designed in such a way that the patient may take one or two tablets per 24h. The dose may also be obtained by the plasters mentioned above or chewable tablets which also may contain flavouring substances, consistency agents and/or any binding agent having an ability to bind nicotine and permit the release thereof at a suitable speed. The nicotine may be present in a substantially free form in such a binding agent, be chemically bounded to any substance or any nicotine compound or as a nicotine derivative.

In contrast to the medicament for smoking cessation, there is no desire of the present invention to obtain any quick addition when the patient suffers from abstinence but rather a slow and over the time uniform dosing speed in order to obtain an equal plasma concentration and bioavailability.

The invention is not limited to the examples given but may be varied and modified within the scope of the following claims.

Claims

1. Use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture
5 of a medicament to be supplied to an individual of a human being or an animal for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.
2. Use according to claim 1, wherein the medicament is supplied
10 via the blood path.
3. Use according to claim 2, wherein the medicament is intended to be administered via the gastrointestinal tract.
- 15 4. Use according to claim 2, wherein the medicament is intended to be administered transdermally.
5. Use according to claim 2, wherein the medicament is intended to be administered intravascularly.
- 20 6. Use according to claim 2, wherein the medicament is intended to be administered intranasally.
7. Use according to claim 2, wherein the medicament is intended
25 to be administered intravaginally.
8. Use according to any one of the preceding claims, wherein said purpose is to counteract pulmonary emphysema.
- 30 9. Use according to any one of the preceding claims, wherein said nicotine-based substance includes substantially pure nicotine.
10. Use according to any one of the preceding claims, wherein said nicotine-based substance includes nicotine derivative,
35 intermediate metabolites of nicotine or degradation products of nicotine.

11. Use according to any one of the preceding claims, wherein said one substance based on nicotine and/or substances produced from said one substance are absorbed by a binding agent.
- 5
12. Use according to any one of the preceding claims, wherein said individual has a congenital bilateral bronchial anomaly.
13. A method for prophylactic or therapeutic treatment of obstructive lung diseases of in individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.
- 10
14. A method according to claim 13, wherein the medicament is supplied via the blood path.
- 15
15. A method according to claim 14, wherein the medicament is intended to be administered via the gastrointestinal tract.
- 20
16. A method according to claim 14, wherein the medicament is intended to be administered transdermally.
17. A method according to claim 14, wherein the medicament is intended to be administered intravascularly.
- 25
18. A method according to claim 14, wherein the medicament is intended to be administered intranasally.
19. A method according to claim 14, wherein the medicament is intended to be administered intravaginally.
- 30
20. A method according to any one of claims 13 to 19, wherein said individual has a congenital bilateral bronchial anomaly.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number
WO 01/15697 A1

(51) International Patent Classification⁷: A61K 31/465

(21) International Application Number: PCT/SE00/01683

(22) International Filing Date:
1 September 2000 (01.09.2000)

(25) Filing Language: Swedish

(26) Publication Language: English

(30) Priority Data:
9903085-0 1 September 1999 (01.09.1999) SE
0001075-1 27 March 2000 (27.03.2000) SE

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,

CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF AT LEAST ONE SUBSTANCE BASED ON NICOTINE AND/OR A SUBSTANCE PRODUCED FROM SAID ONE SUBSTANCE FOR THE MANUFACTURE OF A MEDICAMENT, AND A METHOD FOR TREATMENT OF OBSTRUCTIVE LUNG DISEASES

(57) Abstract: The invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to an individual of a human being or an animal for the purpose of counteracting, in a prophylactic or therapeutic manner, obstructive lung diseases, in particular pulmonary emphysema. The medicament is intended to be supplied via the blood path and to be administered via the gastrointestinal tract, transdermally, intravascularly, intranasally or intravaginally. The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases of an individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.

WO 01/15697 A1

U.S. PATENT & TRADEMARK OFFICE

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(includes Reference to PCT International Applications)

Attorney's docket No. _____

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF AT LEAST ONE SUBSTANCE BASED ON NICOTINE AND/OR A SUBSTANCE PRODUCED FROM SAID ONE SUBSTANCE FOR THE MANUFACTURE OF A MEDICAMENT, AND A METHOD FOR TREATMENT OF OBSTRUCTIVE LUNG DISEASES

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application.

Serial No. _____

on _____

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/SE00/01683 _____

on 1 September 2000 _____

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

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COUNTRY (if PCT indicate PCT)	APPLICATION NO.	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. 119
Sweden ✓	9903085-0 ✓	1 September 1999 ✓	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Sweden ✓	0001075-1 ✓	27 March 2000 ✓	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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Combined declaration for patent application and power of attorney (continued) (includes Reference to PCT International Applications)	Attorney's docket No
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PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
APPLICATION NO	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
APPLICATION NO.	FILING DATE	US SERIAL NO. ASSIGNED (if any)		
PCT/SE00/01683	1 September 2000			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number):

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POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
FULL NAME OF INVENTOR (03)	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201 <u>Donald K. Huber</u>
DATE <u>2002 02 27</u>